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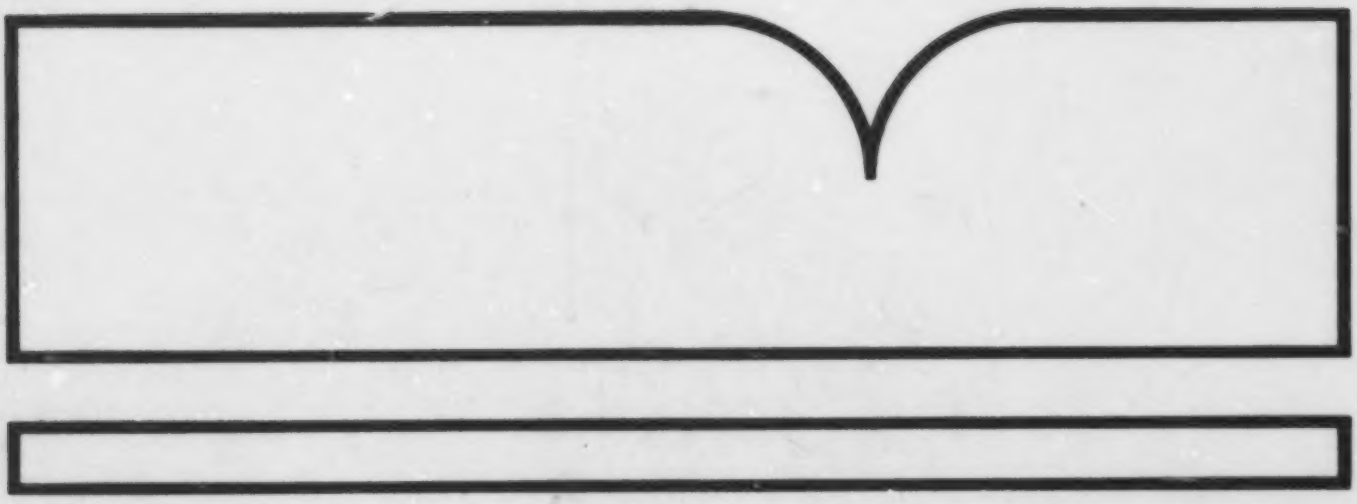

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16. ABSTRACT

Concern as to the toxicity of the oxides of nitrogen has been frequently expressed in clinical and toxicological literature. Oxides of nitrogen are highly reactive compounds and suggest toxic effects on biological systems. The earliest evidence for potential damage to man occurred in the chemical industry where as early as 1804[1] the death of a man and his dog was recorded after breathing nitric acid fumes. Other occupational exposures have been seen with the use of explosives which generated NO_2 during misfires. Welding operations generate substantial quanties of NO_x. Burning of plastics, shoe polish, and nitrocellulose also results in potentially excessive quantities of NO_x. High concentrations of ambient NO_2 were clearly associated with acute pulmonary edema and death. Lowry and Schuman[2] were among the earliest investigators to demonstrate that exposures to NO_2 in excess of 200 ppm. would induce the above effects. Their description of silo fillers disease clearly identified another potential occupationally related effect of NO_2 exposure, but the disorder had been recognized much earlier[3] when in 1914 four individuals died suddenly after entering a recently filled silo. These fatalities were mistakenly attributed to high concentrations of carbon dioxide.

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CONCERN as to the toxicity of the oxides of nitrogen has been frequently expressed in clinical and toxicological literature. Oxides of nitrogen are highly reactive compounds and suggest toxic effects on biological systems. The earliest evidence for potential damage to man occurred in the chemical industry where as early as 1804[1] the death of a man and his dog was recorded after breathing nitric acid fumes. Other occupational exposures have been seen with the use of explosives which generated NO_2 during misfires. Welding operations generate substantial quantities of NO_x. Burning of plastics, shoe polish, and nitrocellulose also results in potentially excessive quantities of NO_x. High concentrations of ambient NO_2 were clearly associated with acute pulmonary edema and death. Lowry and Schuman[2] were among the earliest investigators to demonstrate that exposures to NO_2 in excess of 200 ppm. would induce the above effects. Their description of silo fillers disease clearly identified another potential occupationally related effect of NO_2 exposure, but the disorder had been recognized much earlier[3] when in 1914 four individuals died suddenly after entering a recently filled silo. These fatalities were mistakenly attributed to high concentrations of carbon dioxide. Horvath et al.[4] recently reviewed data accumulated on 23 patients exposed to nitrogen dioxide in agriculture or industrial situations. During the acute phase following exposure, varying combinations of restrictive and obstructive ventilatory defects, impaired diffusion capacity, and hypoxemia were found. Some evidence of pulmonary dysfunction persisted after follow-up

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periods of 2½ to 13½ years, including diminished exercise tolerances with dyspnea on exertion. Fleming et al.[5] made physiologic studies of a patient exposed to nitric acid fumes during the acute (immediate) and delayed (13 weeks later) stages. The acute changes were as anticipated. During the delayed stage, elastic recoil and resistance to flow were normal but dynamic compliance was reduced and dependent upon respiratory frequency and, more significantly, oxygen transport was abnormal during exercise with a $P(A\text{-}a)0_2$ of 20 mm.Hg. Dysfunction of small airways was evident.

Concern for the health effects of lower (ambient) levels of NO_2 developed and the primary approaches to evaluation of such effects utilized techniques which provided data representative of changes observed in individuals exposed to the higher concentrations. Nitric oxide (NO) is the most prevalent nitrogenous compound directly emitted into ambient air from fossil fuel combustion. Several secondary and tertiary compounds, nitrogen dioxide, nitric acid, nitrites, and nitrate aerosols are formed in ambient air as the result of mixing and chemical reactions of NO and other nitrogen oxides with non-nitrogenous substances. (Nitrosamines may also be formed, although the evidence for such requires further effort.) Some concern has been expressed regarding the potential of all of these compounds to induce adverse health effects. Of these, nitrogen dioxide (NO_2) has been most frequently studied and an extensive data base links it to a number of specific health and welfare effects. Generally speaking, the effects of NO_2 on the respiratory system have been most extensively studied, and the potential of this compound to induce both acute and long-term health effects appears to be fairly convincingly documented.

The respiratory system effects of low NO_2 exposures have been delineated by data obtained from controlled human exposures, community epidemiology studies, and animal toxicological experiments. We will be concerned with the first two approaches which have shown alterations in pulmonary function, especially increased airway resistance and increased incidence of respiratory illness. These effects occur from exposures to NO_2 concentrations approaching or falling within recorded ambient air levels of NO_2. Controlled experimental studies in the laboratory have been mostly concerned with exposure to NO_2 alone, although a few studies have considered effects during exposure to one or two additional air pollutants. These clinical studies have generally been conducted on

young, healthy adults or on sensitive subjects, i.e., individuals with chronic respiratory problems. Epidemiologic studies, on the other hand, have been compromised by multiple factors, including the presence of many air pollutants which may not have been determined during the duration of the studies.

NO_2 is an acid anhydride, and reacts with water at ambient concentrations in the air. Despite this hydration, some NO_2 is not removed in the upper airways and penetrates deep into the lung. Studies utilizing short-lived tracers have shown that NO_2 is rapidly taken up and distributed throughout the lung.[6] A significant fraction of NO_2 is retained in the lung, where it presumably reacts with pulmonary tissue by peroxidation and results in direct injury to the lung. Effects may not be noted immediately, being delayed for some time. Repair of injured tissue occurs fairly rapidly.

Controlled experimental exposures of normal subjects to NO_2 have been limited. In an early study, Von Neiding et al.[7] observed significant decreases in lung diffusion capacity (DL_{CO}) in 16 healthy subjects exposed for 15 minutes to 5.0 ppm. NO_2. Von Neiding et al.[8] reported on 13 healthy subjects exposed to NO_2 (0.5 to 5.0 ppm.) for 15 minutes. Pulmonary function measurements indicated that in these healthy subjects effects were observed only during exposure to the highest concentrations of NO_2. They also noted an increased difference between alveolar and arterial P_{O_2}. These investigators also exposed 11 healthy subjects for two hours to 5.0 ppm. NO_2, and observed significant increases in R_{aw} and (A-a) P_{O_2}.[9] The significance of the changes in (A-a)P_{O_2} are questionable, in part due to the techniques employed and some question as to the conditions present in their exposure chambers. Regardless of these questions, the potential of high NO_2 exposure to modify the delivery of oxygen to tissues remains unanswered. As noted later, no evidence for increased oxygen uptake during light to moderate exercise has been found.

Beil and Ulmer[10] did not find a decreased Pa_{O_2} in subjects exposed for two hours to NO_2 (1.0, 2.5, 5.0, and 7.5 ppm.). Significant increases in R_{aw} were found during exposures to 2.5 ppm. and above. Exposure to higher levels of NO_2 produced no further increases in R_{aw} compared to those observed to 2.5 ppm. They further studied subjects exposed for up to 14 hours to 5.0 ppm. and noted that initial R_{aw} increases occurred during the first half hour and tended to return toward normal values in the

first two hours. However, R_{aw} tended to increase again after six to 14 hours. R_{aw} remeasured 10 hours after this prolonged exposure ended had returned to pre-exposure levels.

Abe[11] found increases in both expiratory and inspiratory flow resistance in subjects exposed for ten minutes to 4.0 to 5.0 ppm. NO_2. Effective compliance measured 30 minutes postexposure had decreased some 40% when compared to controls. Similar changes in flow resistances were also observed in subjects exposed for 10 minutes to 0.7 to 2.0 ppm. NO_2.[12] Hackney et al.[13] found no significant changes in pulmonary function in 16 individuals exposed to 1.0 ppm. for two hours. Folinsbee et al.[14] concluded from studies of three groups of five young healthy males that no significant alterations in pulmonary, cardiovascular, or metabolic functions were produced by two hours (with intermittent exercise during the exposure) of exposure to 0.62 ppm. NO_2. Another study by these same investigators[15] of eight subjects exposed to 0.50 ppm. under a variety of ambient temperature conditions with one period of 30 minutes of exercise during the two hours also failed to observe any changes in the above noted functions. Kerr et al.[16] studied 10 normal subjects exposed for two hours to 0.5 ppm. NO_2. One subject had the very mild symptom of slight rhinorrhea. No significant alteration in pulmonary function resulted from the exposure.

Several studies have utilized a challenge with acetycholine further to clarify pulmonary responses to nitrogen dioxide. Von Neiding et al.[9] suggested an increased sensitivity of the bronchial tree to administered acetycholine in subjects exposed to a very low level of NO_2. Beil and Ulmer[10] reported increased sensitivity to acetycholine after a two-hour exposure to 7.5 ppm NO_2 but not after exposure to 2.5 or 5.0 ppm., and further found increased sensitivity to acetycholine in subjects exposed for 14 hours to 5.0 ppm.

Potentially sensitive subjects, patients with asthma or chronic bronchitis, have been studied by several investigators. Von Neiding et al.[8,17] studied 88 individuals with chronic bronchitis. Significant elevations in R_{aw} were seen after 15 minutes exposure to 1.6 ppm. and higher. This decrease became more pronounced at concentrations above 2.0 ppm. and disappeared completely at concentrations below 1.5 ppm. Kerr et al.[16] reported on 13 asthmatics and seven chronic bronchitics exposed to 0.5 ppm. A 15-minute period of light to moderate exercise was undertaken during the two-hour exposure. Seven asthmatics and one bronchitic exper-

ienced symptoms during the exposure, but overall pulmonary function did not significantly decrease.

Orehek et al.[18] studied the effects of low levels of NO_2 exposure on the bronchial sensitivity of asthmatic patients to carbachol, a bronchoconstricting agent. In this study carbachol was used to induce a response in asthmatics similar to the response occurring when they are exposed to particular natural agents to which they are sensitive. Nitrogen dioxide concentrations were monitored by the Saltzman method. For 20 asthmatics, dose-response curves were developed for changes in specific airway resistance (SR_{aw}) as a result of the subjects inhaling carbachol after a one-hour exposure to clean air, and after a one-hour exposure to 190 μg./m.^{3} NO_2 (0.1 ppm.). Following the initial NO_2 exposure, marked increases in SR_{aw} were observed in only three of 20 test subjects, but these three observations, together with smaller increases in 10 other subjects identified after carbachol treatment, gave a small but statistically significant increase in SR_{aw} for the 13. The NO_2 exposure also increased the effect of the bronchoconstrictor in 13 of 20 subjects. The mean dose of carbachol producing a twofold increase in SR_{aw} in the 13 sensitive subjects was decreased from 0.66 mg. to 0.36 mg. as a result of NO_2 exposure. Seven asthmatic subjects showed neither an increase in R_{aw} in response to the exposure to NO_2 nor an enhanced effect of carbachol.

The statistical significance of the above data was affected greatly by the small sample size. For example, the mean dose of carbachol producing a 100% increase in R_{aw} was 0.35 mg. for seven nonresponders and 0.66 mg for 13 responders. However, the dose difference was not statistically significant. On the other hand, the mean doses of carbachol producing a 100% increase in R_{aw} for 13 responders, before and after the NO_2 exposure, were 0.66 mg. and 0.36 mg. respectively. In this instance, the same difference in means was statistically significant. Similarly, a 15% difference in mean R_{aw} for 13 responders, before and after NO_2 exposure, was significant statistically, but a 20% difference in the initial mean between responders and nonresponders was not significant. Some questions as to the significance of these findings must be raised, and duplication is necessary.

Studies on the interaction of nitrogen dioxide with other ambient pollutants are limited. Von Neiding et al.[19] exposed healthy subjects to a combination of NO_2 (0.05 ppm.), O_3 (0.025 ppm.), and SO_2 (0.11 ppm.) for two hours. No effect on R_{aw} or $(A\text{-}a)P_{O_2}$ was found. These investiga-

tors also exposed subjects to NO_2 (5.0 ppm.) and O_3 (0.1 ppm.) for two hours. Significant decreases in both R_{aw} and in intermittently exercising (A-a)P_{O_2} were observed following NO_2 exposures, but were not further altered in the combined NO_2-O_3 condition. Hackney et al.[20] exposed four healthy "ozone sensitive" subjects to a pollutant combination consisting of O_3 (0.3 ppm.), NO_2 (0.3 ppm.), plus carbon monoxide. They were exposed for four hours plus one additional hour during which pulmonary functions were measured. The total exposure time was approximately twice that experienced in the ambient conditions present in the Los Angeles basin. Minimal alterations in pulmonary functions to O_3 alone were observed, changes were not further influenced by exposure to the combined pollutants. Another group of seven men (including some believed to be unusually reactive to respiratory irritants) were exposed for two hours to O_3 (0.25 ppm.) and NO_2 (0.3 ppm.). Little or no change in pulmonary function was found with ozone exposure alone or with the combination.[20] Nakamura[21] exposed two groups of seven and eight resting young subjects for five minutes to 1,400 μg./m.^{3} sodium chloride aerosol. This was followed by a five-minute exposure to 3.0 or 6.0 ppm. NO_2. After another 10-15 minute rest period they were exposed to a combination of NO_2 and sodium chloride at the above concentrations. Each group exhibited increased R_{aw} after exposure to NO_2 alone. The sodium chloride aerosol exposure resulted in no changes but in the combination exposure 40% greater increase in R_{aw} was observed. We[15] exposed eight young adults either to filtered air or to 0.5 ppm O_3 plus 0.5 ppm. NO_2 in filtered air under four different environmental conditions: 1) 25°C , 45% rh.; 2) 30°C., 85% rh.; 3) 35°C., 40% rh. and 4) 40°C., 50% rh. Each subject had a total of eight exposures, with a minimum of one week between exposures. During the exposures the subject first rested for 60 minutes, then exercised for 30 minutes at 35-40% of his predicted maximum aerobic capacity, and then rested for the final 30 minutes. Repeat tests were generally made on each subject at the same time of the day. Figures 1 and 2 illustrate the changes observed in $FEV_{1.0}$ and maximal midexpiratory flow (FEF 25-75%). The pulmonary responses to ozone alone were as found in previous studies by our group. No synergism or interaction between ozone and nitrogen dioxide was observed.

Epidemologic studies concerned with the increased risk of acute respiratory disease and diminished lung function in individuals exposed to community air can be conveniently divided into two groups, i.e., the

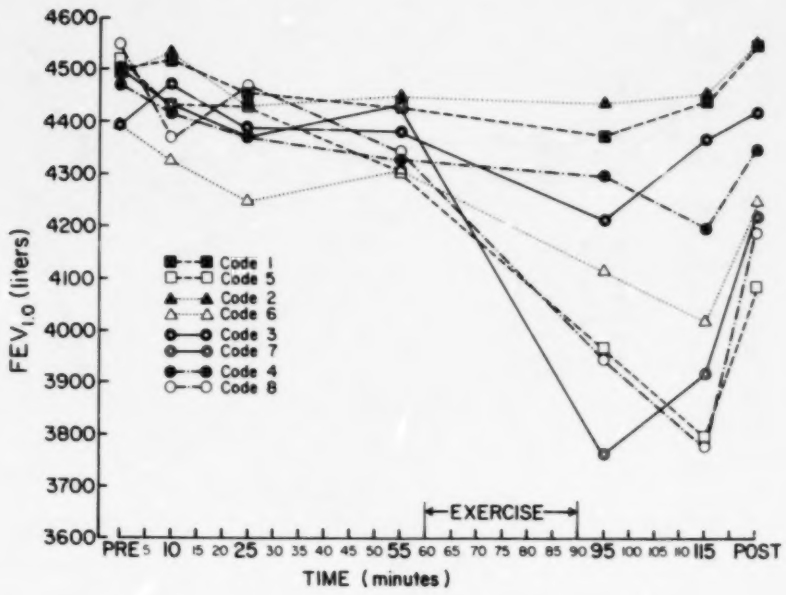

Fig. 1

effects on adults and on children. Additional concern has been expressed over the effects of indoor exposure. Community air contains multiple pollutants in varying concentrations. In most cases it is difficult, if not impossible, to determine whether a given level of NO_2 was responsible for the observed health effects or whether other pollutants separately and in combination with NO_2 were responsible. It has also been difficult to determine actual exposure of study populations to pollutants. Nonetheless, some limited evidence does exist relating pulmonary functions to NO_2 exposure.

Combustion of natural or manufactured gas within confined spaces increases NO_2 concentrations. A number of studies of indoor levels of this pollutant have been reported, but only the most recent, by Keller et al.,[22] Melia et al.,[23] and Speizer et al.[24] comparing NO_2 levels in homes utilizing either gas or electric stoves will be cited. Peak NO_2 concentrations of from 0.25 to 1.0 ppm. were frequently found either in the kitchen or in nearby rooms using gas stoves. The ranges in concentration were quite large, however. Nonetheless, 24-hour average values indicated that NO_2 levels were four to seven times higher in homes with gas stoves than

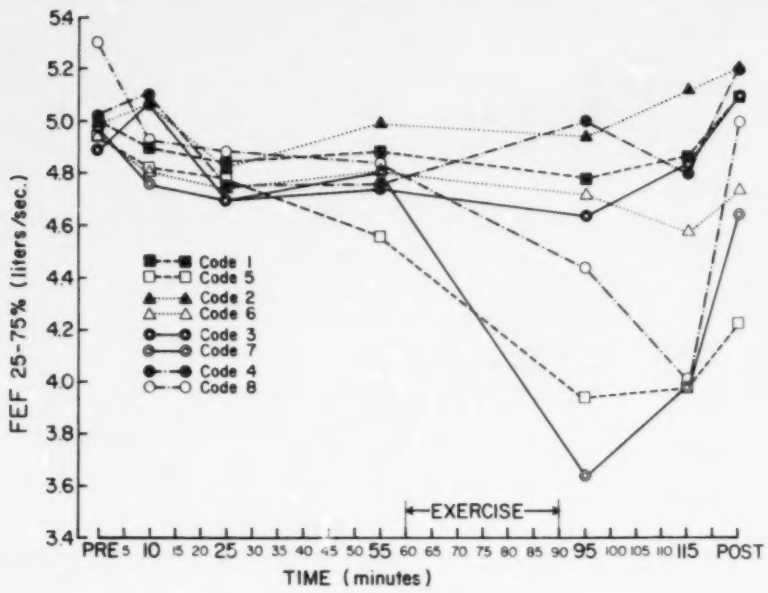

Fig. 2

in homes with electric stoves. The average 24-hour NO_2 levels for gas utility homes was below current federal 24-hour outdoor standards. The presence of other pollutants, including particulates, and the influence of smokers on the composition of indoor materials somewhat complicates the interpretation of data obtained from community studies of indoor exposure. It should also be noted that such evaluation of pollutant levels was not necessarily obtained in homes whose residents were studied for the effects of the pollutants.

The incidence of respiratory disease among housewives cooking with either gas or electric stoves was reported by two groups.[23,25,26] Neither Long Island housewives[25] or Columbus, Ohio housewives[23,26] exhibited any difference in incidence of respiratory disease. In the latter groups, cooking with gas was not associated with a decrease in pulmonary function (FVC and FEV-75).

Children were also evaluated[23,26] in the Columbus study, again with no evidence of increased respiratory disease. On the other hand, Melia et al.[27] reported an increased illness rate in children living in homes with gas stoves when compared to children living in homes with electric stoves.

The prevalence of bronchitis was 5.7% and 4.7% for boys and girls, respectively, in the gas-supplied homes, versus a rate of 3.1% and 2% in homes with electric stoves. Although the contribution of family smoking habits could not be determined, investigators related this factor to social class, and pollutants were not measured at the time of these observations. Speizer et al.[24] have recently reported similar data from their six-city study taking into account the question of family smoking and, to some degree, a better concurrent evaluation of pollutant levels. Very small but statistically significant lower values for FVC and $FEV_{1.0}$ were found in children whose homes had gas cooking stoves. In general these investigators confirmed Melia et al.'s findings of a relationship between gas stove use and illness in children, but adjustments for other factors tended to reduce the association found.

Community studies such as those conducted by Shy et al.[28-30] in Chattanooga, Tenn., were designed to evaluate changes in pulmonary function of children living in high, intermediate, or low concentrations of NO_2. Results proved of questionable significance because of a number of uncontrollable factors. Hasselblad[31] later conducted studies in the same area. His data indicated that the population living in the intermediate and low pollution area had no statistically significant impairment of pulmonary function. Shy et al. also evaluated the frequency of acute respiratory disease among children and parents living near a large point source of nitrogen dioxide (plus other pollutants) and other families in areas with low NO_2 concentrations. Although the incidence of acute respiratory disease was found to be higher in the vicinity of the high NO_2 levels, other factors (including other pollutants) could not be parceled out, and the relationship to high NO_2 remains unclear. Pearlman et al.[32] later performed a retrospective study in the same Tennessee area. Bronchitis rates per hundred children were highest in areas of maximum NO_2 concentration.

Utell et al.[33] examined the potential synergy between acute exposure to a pollutant (sodium nitrate aerosol) and acute respiratory infections. The mass median aerodynamic diameter of the aerosol was 0.49 μm; the concentration 7,000 $\mu g./m.^3$ Eleven previously healthy adults with uncomplicated influenza A (H_1N_1) were studied at the time of acute illness and 1, 3, and 6 weeks later. Significant decreases in specific airway conductance and partial expiratory flows at 40% of total lung capacity were observed at the initial examination and one week later. By the third

week, inhalation of sodium nitrate no longer changed airway function. Control studies were made with a sodium chloride aerosol. They concluded that individuals with acute respiratory disease were susceptible to bronchoconstriction from this air pollutant—one that normally did not influence airway function.

A number of additional community studies have been conducted to determine the role of NO_2 in altering the extent of pulmonary disorders by evaluating changes in pulmonary function and prevalence of chronic respiratory disease. Speizer and Ferris[34] studied policemen in urban Boston. Cohen et al.[35] looked at Seventh Day Adventists in two communities differing in pollution levels. Chapman et al.[36] reported on housewives in Chattanooga, while Linn et al.[37] compared the incidence of respiratory disease in women living in either Los Angeles or San Francisco. In Japan, Kagawa et al.[38] and Kagawa and Toyoma[39] evaluated pulmonary function changes in normal school children. Japanese housewives were also studied.[40,41] Other studies have been reported from the Soviet Union. These studies do not provide convincing information for or against a relationship between NO_2 levels, pulmonary function changes, and prevalance of respiratory disorders.

Controlled experimental studies suggest that increased airway resistance occurs in healthy young individuals exposed for a brief period to NO_2. Bronchitic and asthmatic individuals also respond to NO_2 in a similar manner. There is considerable confusion as to the precise levels when these responses occur, suggesting the need for further investigations. Most studies have utilized a single acute exposure, and consequently the potential for greater or smaller changes in airway resistance with repeated exposures cannot be determined. Epidemiologic studies have not provided sufficient information adequately to characterize the influence of NO_2 as a primary factor in altering the prevalance of respiratory disorders. Nitrogen dioxide is toxic to man, but its precise role at ambient levels requires further clarification.

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